UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/383,978	08/26/1999	HEINZ SCHALLER	BBI-102CP	7239

28157 7590 07/28/2002

URSULA B. DAY, ESQ.
350 FIFTH AVE.
SUITE 3220
NEW YORK, NY 10118

EXAMINER	
NGUYEN, QUANG	

ART UNIT	PAPER NUMBER
1636	17

DATE MAILED: 07/28/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/383,978	Applicant(s) SCHALLER ET AL.	
	Examiner Quang Nguyen, Ph.D	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 May 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,33-39 and 41-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,33-39 and 41-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet* .

DETAILED ACTION

Applicants' amendment filed May 09, 2002 in Paper No. 14 has been entered.

Claims 1-8, 33-39 and 41-50 are pending in the present application, and they are examined on the merits herein.

The text of those sections of Title 35 U.S.C. Code not included in this action can be found in a prior office action.

Claim Objections

Claims 33, 37, 39, 43 are objected to because they contain the abbreviations "RC" and "RII" that should be written out at the first occurrence of the terms. Appropriate correction is required.

Examiner would like to note that amended claims 38 appearing in the clean version and version showing changes do not match as they are presented in Applicants' amendment filed on August 29, 2001 in Paper No. 11. Appropriate correction is required.

Claim Rejections - 35 USC § 112

Amended claims 1 and 37-38 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of expressing a heterologous gene in hepatocytes *in culture* comprising:

(a) providing replication defective hepadnavirus particles at a titer level competent to infect hepatocytes, wherein the S-gene in the genome of said replication

defective hepadnavirus particles has been replaced with the heterologous gene of up to 800 nucleotides in length such that expression of the heterologous gene is regulated by the S-promoter; and

(b) infecting hepatocytes with said replication defective hepadnavirus particles such that the heterologous gene is delivered into the hepatocytes and expressed in the hepatocytes; and wherein the replication defective hepadnavirus particles are one of human heptatitis B virus or duck hepatitis B virus particles;

does not reasonably provide enablement for other embodiments of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for the same ground of rejection set forth in the previous Office Action.

Amended claim 1 is drawn to a method for expressing a heterologous gene in hepatocytes comprising: providing replication defective hepadnavirus particles at a titre level competent to infect hepatocytes, wherein a region of the preS or S-gene of the hepadnavirus genome has been replaced with the heterologous gene such that expression of the heterologous gene is regulated by regulatory sequences of the preS or S-gene; and infecting hepatocytes with the hepadnavirus such that the heterologous gene is delivered into the hepatocytes and expressed in the hepatocytes, and wherein the replication defective hepadnavirus particles are one of human hepatitis B virus or duck hepatitis B virus particles.

Amended claims 37-38 are drawn to a pharmaceutical composition comprising: a replication defective hepadnavirus of the group consisting of human hepatitis B virus and duck hepatitis B virus with a region of one of its pre-S-genes or S-genes deleted and replaced with a heterologous gene such that the sequences of the RC or RII that are essential for reverse transcription are retained, and a pharmaceutically acceptable carrier; the same further comprising a helper virus.

The specification teaches by exemplification the preparation and production of recombinant replication defective duck and human hepatitis B virus (rDHBV and rHBV, respectively) stocks. The specification further discloses that an efficient transfer and stable expression of the marker GFP gene operably linked to DHBV S-promoter could be established for viable cultured hepatocytes. In addition, the delivery of a transgene mediated by rDHBV has been shown to be both hepatocyte and species-specific as shown by the lack of GFP expression in non-parenchymal cells, primarily sinusoidal endothelial cells and Kupffer cells constituting about 15% of the total cell population in the primary hepatocyte cultures, and in primary mouse hepatocytes. Moreover, intravenous injection of rDHBV-GFP in ducklings resulted in the recovery of GFP-fluorescent hepatocytes 7 days post infection, indicating a successful *in vivo* gene transfer mediated by rDHBV-GFP. The specification further teaches that rDHBV can superinfect DHPV-infected cultured hepatocytes, but the transduction efficiency is 20-fold lower compared to hepatocyte cultures not preinfected with DHBV. Additionally, superinfection of cultured DHPV-infected hepatocytes with rDHBV-IFN resulted in a decrease in DHBV production relative to untreated controls, indicating that the inhibition

was caused by the expression of transduced IFN transgene. Similarly, human rHBV was shown to infect cultured primary human hepatocytes comparable to wild type HBV, and that the delivery of a transgene mediated by rHBV is species and hepatocyte-specific *in vitro*.

The above evidence has been noted and considered. However, the evidence is not reasonably extrapolated to the instant broadly claimed invention.

With respect to pharmaceutical composition claims, when read in light of the specification the sole purpose for the use of such pharmaceutical compositions is for treating a subject having a hepatic disorder or a hepatitis infection by providing an effective level of a therapeutic gene product, preferably a cytokine, more preferably IFNα, TNFα, IFNβ, IL-18 and IFNγ. As enablement requires the specification to teach how to make and ***use*** the claimed invention, the instant specification fails to enable the use of the instant pharmaceutical compositions for the following reasons. This is because at the effective filing date of the present application, the art of gene therapy was still considered to be highly unpredictable and immature. Dang et al. (Clin. Cancer Res. 5:471-474, 1999) noted several known factors limiting the effectiveness of gene therapy and these include the lack of optimal vectors, host immunological responses to the vectors, the lack of long term and stable transgene expression *in vivo*, as well as an efficient transgene delivery to target tissues (page 474, column 2, lines 4-9 of the last paragraph). Dang et al. further stated that "This work shop reviewed some recent advances in gene delivery, gene expression, immune manipulation, and the development of molecular targets and stressed that all of these fields will need further

advancement **to make gen therapy a reality**" (page 471, column 1, last sentence of first paragraph). The instant specification fails to provide sufficient guidance or direction regarding to the use of any replication defective recombinant hepadnavirus particles of the presently claimed invention to achieve any therapeutic effects. The specification fails to provide a nexus between the expression of a marker gene GFP in hepatocytes *in vivo* and the desired therapeutic results for treating a subject having a hepatic disorder or a hepatitis infection using the presently claimed pharmaceutical compositions. Since the prior art at the time the invention was made does not provide such teachings, it is incumbent upon the present specification to do so. Even a year after the effective filing date of the present application, therapies utilizing IFN-α and nucleoside analogues are only available for treating hepatic diseases (Protzer et al., Proc. Natl. Acad. Sci. 96:10818-10823; 1999; IDS). Moreover, Ganem (Proc. Natl. Acad. Sci. 96:11696-11697, 1999; Cited previously by Applicants) stated "We are, therefore, still a long way from the routine use of hepadnaviruses in gene therapy" (page 11697, col. 3, top of first full paragraph). Given the apparently low *in vivo* transduction rates reported in this application (1 GFP-positive cell per 10^4 to 10^5 hepatocytes and at least 20-time less efficient for preinfected hepatocytes for the rHBV particles), the instant specification fails to demonstrate that at such low transduction rates an effective amount of hepatocytes in treated livers could still be infected with the recombinant hepadnavirus of the presently claimed invention to express effective levels heterologous gene products to yield the desired beneficial effects. It should be further noted that adverse host immune responses reactive against administered recombinant

hepadnavirus particles can further reduce the effective expression levels of heterologous genes to yield the therapeutic effects contemplated by Applicants. Due to the lack of guidance provided by the instant specification, it would have required undue experimentation for a skilled artisan to make and **use** the instant broadly claimed pharmaceutical compositions.

The instant claims encompass the replacement of a region of the preS or S-gene with a heterologous gene of any length. It is noted that the term a "region" of a gene refers to the length of nucleotide sequence of the hepadnavirus genome that is replaced by a heterologous gene not necessarily limited to any particular length (see instant specification, page 12, lines 8-13). The instant specification is not enabled for such a broadly claimed invention. This is because apart from the exemplification of disclosed rDHBV and rHBV particles, the instant specification fails to provide sufficient guidance for a skilled artisan on how to generate high titers of replication defective recombinant hepadnavirus particles containing any heterologous gene larger than 800 nucleotides, and at replacement sites other than the S gene of the hepadnaviral genome. For example, the specification fails to teach specifically which cis-acting control elements, internal promoters or enhancers and in which combinations should be maintained in order to achieve at least the titers obtained for rDHBV and rHBV particles, and which additional genomic segments to be deleted or replaced so as to increase the size of incorporated heterologous gene. A hepatitis B virus (HBV) based vector is well known for its size constraint. Protzer et al. (Proc. Natl. Acad. Sci. 96:10818-10823; 1999; IDS) stated "Despite these precautions (with respect to care taken not to exceed the

authentic genome size an not to affect cis-acting control elements), among the several constructs in which different genome segments were replaced, **only substitution of the small envelope (S) gene by foreign sequences turned out to be successful**" (page 40820, col. 2, bottom of first paragraph). Moreover, Ganem also stated "The biggest problem has been the fact that the tiny hepadnaviral genome (3 kb) is virtually blanketed with critical cis-acting elements—initiation sites for minus and plus strand DNA synthesis, promoter elements for multiple critical transcripts, and numerous sequences affecting RNA transport, processing, stability, and packagaing." (page 11696, col. 3, middle of the last paragraph). Therefore, with the lack of sufficient guidance of the present disclosure, it would have required undue experimentation for a skilled artisan to make and use the instant broadly claimed invention.

The courts have stated that reasonable correlation must exist between scope of exclusive right to patent application and scope of enablement set forth in the patent application (27 USPQ2d 1662 *Ex parte Maizel.*).

Accordingly, due to the lack of guidance provided by the specification regarding to the aforementioned issues, the amount of experimentation necessary, the unpredictability of the gene therapy for attaining therapeutic effects, and the breadth of the instant claims, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

Amended claims 33-36, 39 and 41-50 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of producing

replication defective hepatitis B virus particles of human hepatitis B virus and duck hepatitis B virus at a titer suitable for infecting hepatocytes in culture, wherein the S-gene in the genome of said hepatitis B virus particles has been replaced with the heterologous gene of up to 800 nucleotides in length such that expression of the heterologous gene is regulated by the S-promoter; the same replication defective hepatitis B virus particles and their recombinant genomes; does not reasonably provide enablement for other embodiments of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for the same ground of rejection set forth in the previous Office Action.

Amended claims 39 and 41 are directed to a method of producing replication defective hepadnavirus particles of human hepatitis B virus and duck hepatitis B virus at a titer suitable for infecting hepatocytes in culture comprising: co-transfecting hepatocyte cells of a hepatoma cell line with: (i) replication defective hepadnavirus constructs, wherein a region of one of a pre S or an S-gene of the hepadnavirus DNA has been replaced with a gene encoding a heterologous gene while retaining one of an RC or RII signal, such that the expression of the gene encoding a cytokine is regulated by regulatory sequences of the S-gene; and (ii) a helper construct for transcomplementing lacking viral gene products; culturing the hepatocytes until infectious viral particles are produced; and recovering the infectious particles.

Amended claims 42 and 2-8 are drawn to drawn to a method for producing replication defective recombinant hepadnavirus particles capable of expressing a

heterologous gene in hepatocytes in culture comprising: replacing an S-gene in a hepatitis B virus genome with the heterologous gene such that the expression of the heterologous gene is regulated by an S-promoter; producing a replication deficient hepadnavirus by means of a helper plasmid transcomlementing viral gene products such that the lacking viral gene products are present; infecting hepatocytes with the recombinant hepadnavirus in culture, whereby the heterologous gene is delivered into the hepatocyte and expressed in the hepatocyte, wherein the replication defective recombinant hepadnavirus particles are human hepatitis B virus particles.

Amended claims 33-36 and 49-50 are directed to a replication defective hepadnavirus particle of the group consisting of human hepatitis B virus and duck hepatitis B virus, wherein a region of a pre-S and S-gene of the hepadnavirus genome have been deleted and replaced by a heterologous gene such that the sequences for RC and RII that are essential for producing reverse transcriptase are retained.

Amended claims 43-48 are directed to a recombinant HBV genome, wherein an S-gene in the HBV genome is deleted and replaced by a heterologous gene and wherein the genome is selected from the group consisting of recombinant human hepatitis B virus or recombinant duck hepatitis B virus, and wherein the sequences for RC and RII that are essential for reverse transcription are retained.

The specification is not enabled for the instant broadly claimed invention for the same reasons already set forth in the rejection of claims 1 and 37-38 above. With the lack of guidance provided by the instant disclosure, it would have required undue experimentation for a skilled artisan to make and use the instant broadly claimed

invention, specifically for replacing any heterologous gene larger than 800 nucleotides in length and for deleting and replacing at any sites other than the S gene of the hepadnaviral genome.

Response to Arguments

Examiner noted that Applicants failed to address the above issues (pharmaceutical compositions, length of the inserted heterologous gene and replacement sites other than the S gene of the hepadnaviral genome) in the Amendment filed on May 09, 2002 in Paper No. 14 (pages 14-15).

Accordingly, the above rejections are maintained for the reasons of record.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Amended claims 33-36, 39, 41 and 43-50 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the same ground of rejection set forth in the previous Office Action.

In amended claims 33-36 and 43-50, it is unclear what is encompassed by the phrase "the sequences for RC and RII that are essential for reverse transcription are retained". Since the abbreviations RC and RII are not spelled out in the instant specification, it is unclear what they represent. Additionally, as written does human hepatitis B virus actually contain sequences for RII? The metes and bounds of the claims are not clearly determined. Clarification is requested.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 39 recites the broad recitation "a heterologous gene" and the claim also recites "such that the expression of the gene encoding a cytokine" which is the narrower statement of the range/limitation.

Response to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on May 09, 2002 in Paper No. 14 (page 15) have been fully considered.

Applicants mainly directed Examiner to page 5, lines 33 of the specification and Figure 2, where the abbreviations RII and RC are supposedly defined. Apart from a region labeled RII shown in Figure 2 for pg RNA duck HBV, Examiner can not find any where on pages 5-6 and Figure 2, where the abbreviations RC and RII are spelled out,

particularly for the term "RC". Examiner has no ideas what these abbreviations stand for other than cis-acting regions that are essential for reverse transcription as asserted by Applicants.

Conclusions

Claims 1-8, 33-39 and 41-50 are free of prior art. The prior art did not teach or fairly suggest the presently enabled claimed invention as evidenced by the teachings of Ganem (PNAS 96:11696-11697, 1999, see page 11697, col. 1, first full paragraph) and Protzer et al. (PNAS 96:10818-10823, 1999; see page 10820, col. 2, last sentence of the first paragraph).

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, Dave Nguyen, may be reached at (703) 305-2024, or SPE, Irem Yucel, Ph.D., at (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to Patent Analyst, Tracey Johnson, whose telephone number is (703) 305-2982.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1636.

Quang Nguyen, Ph.D.

DAVE T. NGUYEN
PRIMARY EXAMINER

Continuation of Attachment(s) 6). Other: Notice Re; Power of Attorney & Filing receipt.